TOPICAL COMPOSITION IN THE FORM OF A GEL FOR TREATING SKIN BURNS

FIELD OF THE INVENTION

The present invention relates to a novel topical composition for the local treatment of burns, abrasions, erythema, eczema, herpectic infections, avulsions and any sphacelus causing skin injury and particularly to a composition which forms a clear colloidal film over the injury covering the nerve endings (pain relief), reducing nerve irritation, insulating if from the surrounding environment to avoid contact with harmfulsubstances, and the injury dry and exerting pressure (dressing effect) to create a medium that will enable fast and effective cell regeneration, while the enzymatic effect reduces inflammation, debrides and cleans the zone.

BACKGROUND OF THE INVENTION

MEDICAL AND CLINICAL ENVIRONMENT

Traumatic injuries of skin, such as burns, scalds, abrasions, avulsions, etc., have been studied and treated by the specialized branch of medicine of plastic surgery, involved in the issue under a scientific perspective and in related researches.

Reconstructive and burn surgery, an applied science being part of the plastic surgery specialty, is a field where a specialized physician endeavors to reconstruct tissues, treat burns and repairing skin layers when lost.

In the case of superficial skin injuries and burns, despite a well-known physiopathology, there has not been and there still is not, at the beginning of the XXI century a general consensus as to the treatment of same, thus evidencing the lack of a deeper understanding of issue, while a great number of physicians act empirically or based on very basic information.

This situation has led to the sale, application and prescription as treatment in this field of medicine of a wide variety of products having different sources, from home-made preparations, herbs, , coffee, albumen, Aloe vera, mucilage, etc., to tannins, mercurial preparations and topical antibiotics. The above is the breadth of substances used for treating skin injuries due to burns (or abrasions), which further shows the absence of unanimous consensus in this respect.

The focus of such methods has commonly become antibiotic and cicatrization therapy employing a wide variety of substances, among which we find sulfas, furazolidone, tetracycline, gentamicin, mercurochrome, epithelial growing factor and tannins, whose effects have been studied and are well known. However, the treatment of the main symptoms (pain, inflammation, debriding effect) in a local form has not received any substantial pharmacological attention.

Antibiotic substances such as silver sulfadiazine, furacine (fucidin), terramycin and other types of substances have tried to fill this gap in medical therapeutics.

Unquestionably, silver sulfadiazine has enjoyed a greater success and has acquired a bigger market share. However, from a scientific viewpoint, it is a product far from perfect for treating non-infected skin injuries.

The underlying concept is that these injuries heal by themselves (epithelialization), regardless of the substance used, provided no complications arise.

The object is thus to make the patient as comfortable as possible while his/her own body undergoes the cicatrization process.

BURNS AND AVULSIONS

A burn is defined as the skin injury sustained from the transfer of energy from a thermal source to the body which is large enough to cause injury and which may result from direct conduction (heat), chemical injury or electromagnetic radiation (electrical).

Immediate clinic manifestations of a burn are changes in skin color from erythema to necrosis, intense pain in surperficial cases and presence of bodily fluids by transudation.

A burn occurs when skin cells are destroyed by heat, thereby liberating nerve stimulating chemical substances that cause pain, producing the disruption of the skin and exposing the underlying elements and, depending on the depth, loss of fluids by evaporation.

The healing mechanism of a burn is similar to that of a wound or abrasion, in second degree burns, serum blisters are formed that act as a protective cover while underneath it a new skin layer is being formed from the sides of the burn.

If a burn is too big or remains exposed, it becomes easier for bacteria to enter the body.

Accordingly there are many factors that come into play such as skin disruption, necrosis (death) of the affected skin sector, severe pain, the body's hydro-electrolitic response, inflammation due to presence of fluids and chemicals, blushing due to vasodilatation and the subsequent possibility of bacterial colonization.

Likewise, the defense mechanisms against heat are brought into action: profuse perspiration for lowering the temperature by evaporation with loss of fluids, heat dissipation by vasodilation and resistance of tissues to the heat or radiation (mainly muscles and skin, nerves and vessels are very sensitive). It is considered that no cell damage occurs at temperatures of up to 44°C unless there is very prolonged exposition.

EPIDEMIOLOGY

Burns are some the most frequent injuries experienced by human beings. In the United States from 3.5 to 4 million people go the doctor for diagnostic and treatment of burns.

Burns account for a large percentage of visits to emergency rooms and physician's offices, 8 out of 10 persons experience a burn of some sort every year, being 95% of all burns subject to home or ambulatory treatment .

After a burn occurs and there is cell death, a series of events starts that bears some resemblance to that of wounds:

1- Inflammation: is the normal acute reaction of tissues after injury, immediate response is vasoconstriction by nervous stimulus and thrombosis.

2- Subsequently, there is vasodilatation and increase in capillary permeability during the following 12 to 48 hours, according to the degree of injury, with secretion of plasma or blood fluids containing proteins, electrolytes and water.

The main protein is albumin giving the oncotic pressure (liquid retention) of the plasma and which moves to the extra-vascular space in the burn while retaining liquids in what is known as edema.

With the cell migration, due to the increase in capillary permeability, specialized cells in injury response arrive: leucocytes (macrophages and neutrophils (immune

white cells of the bloodstram) in charge of cleaning and disinfecting the area, a system of defense against bacteria and elimination of dead cells).

Regarding chemical substances, dead cells, plasma and neutrophils produce some chemicals such as: euglobin, (capillary permeability), catecholamine, leucotaxine, bradykinin, kallidin, kallikrein, histamine, serotonin and prostaglandins, all of which cause nervous stimulation, immune cell activity, vasodilatation, cell migration (chemotaxis) and other inflammation related changes.

BURN CLASSIFICATION

It is important to know how burns are classified according to their cutaneous depth, etiology and extension.

Burns are classified according to diagnosis, treatment and prognosis parameters.

a) DEPTH

It is divided into three categories:

- First degree:

First degree – Superficial: only the stratum corneum or outer layers of the epidermis are affected. It is characterized by an erythema or red color, severe pain, local heat, contact and air sensitivity and spontaneous healing in three to four

days. It may cause skin hyperpigmentation. Sunburns are an example of this type of burns: healing occurs in a few days without scarring.

-Second Degree:

Superficial: partial or complete injury to the epidermis but with intact epidermal attachments and indentations, severe pain, erythema, phlyctene, fast capillary filling, skin still soft. Examples of this type of burns are scalds, which heal in 8 days.

Deep: complete epidermis destruction (including stratum germinativum) and part of the dermis, phlyctenas, light rose tone, moderate pain (due to nerve destruction), hardened and withered skin, slow capillary filling and slow healing originated from the attachments (hairs and glands), and almost always leaving a scar. Examples of the above are steam and flame burns, which heal in 16 days.

-Third degree:

The skin is entirely compromised, there is no cell regeneration, white, insensible, withered, dry skin without edemas and may compromise organs other than skin, such as in electric, chemical and fire burns.

These burns always require specialized medical treatment.

First and second degree superficial burns undergo spontaneous healing and are the main subject matter of application of the composition in the present invention.

ETIOLOGY

Determining the origin of the burn is very important to define the intensity, treatment and prognosis of the injury.

Sun, biological, steam, flame and scald burns produce the more superficial burns, direct fire and chemicals burns cause intermediate burns and contact burns, deflagration and electric burns are the most dangerous.

CONSIDERATION AND DISPOSITION OF BURNS

-EXTENSIVE BURNS:

Critical burns:

These burns involve more than 25% of the body in adults and more than 10% in children and exceeding the second degree in depth. In addition to local injuries such as necrosis, pain, vasculitis, edema, transudation and overinfection, there is a systemic compromise which leads to immunological reactions, vasodilation, exit of liquids to the interstitial space, loss of proteins, necrotic residues, general sepsis and compromise of the vascular and urinary systems. In these cases, patient treatment is exclusively managed by physicians and hospitals with liquid, proteins and electrolytes replacement, in-hospital care of wounds and affected systems (airways systems) and in cases of increased depth surgical treatments with grafts, flaps and reconstructive surgical processes. These patients heal slowly and may spend a long time in the hospital. Hypertrophic scars, deformations and hair loss are some of the possible sequelae. Patients who have inhaled smoke are subject to special care as this may lead to injury of the airways, respiratory insufficiency

and death. Antibiotic treatment of both the wound and in general is indispensable as any patient with extensive burns suffers overinfection.

SMALL, MINOR AND SUPERFICIAL BURNS.

A superficial burn is understood as one that can be treated ambulatory at home or at a doctor's practice without complications and does not exceed 25% TBSA and superficial second degree in adults, and 10% superficial second degree in children.

According to the parameters established, these are burns in which there is no hydroelectrolitic compromise of the body, the immunological and vascular compromise is minor, and there is no infection, except for overlapping conditions.

In these cases, treatment is focused on preventing an overinfection, loss of liquids, reducing inflammation of the zone, providing comfortableness, analgesia, cleaning the zone, covering the burn area and protecting it from the environment while the intrinsic healing processes occur.

If a burn is small, shallow and free of complications, the treatment consists of covering, cleaning, examining, and washing the zone, soothing the pain and debriding such zone, while preventing any overinfection and allowing reepithelialization and complete healing in a period from 3 to 5 days maximum. Use of analgesic, antibiotic substances and other products is avoided as local cover. The novel composition subject matter of this invention has been designed for this local treatment of a burn.

OBJECTIVES OF BURN TREATMENT

The objectives of the local treatment of burns are protecting against infection and trauma, soothing the pain, reducing inflammation and accelerating the removal of dead tissue, while promoting methods that accelerate cicatrization. Superficial burns that epithelialize faster do so with less scar.

Nowadays, the most common methodology for treating superficial burns includes generally the use of topical antimicrobial agents, preferably of silver sulfadiazine (SSD). This drug was developed in the 60's and is effective for controlling microbial growth in the burn as the eschar separates. SSD has a hydrophobic molecule that makes the application of the cream induce the accumulation in significant amounts of proteinaceous exudates over the wound surface.

These exudates are called PSEUDOESCHAR. It is necessary to undertake efforts to remove this pseudoeschar, which is a strong layer of material on the burn surface, for paradoxically bacterial colonization can otherwise advance. Therefore the use of SSD in burns should be accompanied by periodical surgical debriding for removing the eschar and accumulated proteinaceous necrotic residues.

The epithelialization process requires the burned zone to be clean and free of any debris, requiring in the case of SSD the removal of necrotic tissue, which unfortunately can be extremely painful and stressing for the patient, and further requires the use of great doses of analgesic.

Endogenous proteases are produced by various cells in a burned zone. These enzymes promote the liquefaction and removal of necrotic tissue; the devitalized protein residues must be removed in order to allow the epithelial cells to migrate and repair the surface of the burn. Collagenases are intrinsically produced proteases (enzymes) that act exclusively on the collagen by denaturizing it and making it easily degradable by less specific proteases.

For several decades exogenous protease preparations have been made to accelerate the debriding process of burns and lesions while increasing the local protein degradation rate and thus accelerating the epithelialization process. This translates into a reduction of intensity of the lesion, less care hours of the injury , and less discomfort for the patient. Exogenous collagenase can be obtained from an enzymatic preparation derived from the clostridium histolyticum bacteria.

PAIN AND TRAUMA OVER THE BURN OR SUPERFICIAL ABRASION

During the 12th annual congress of the European Wound Management Association held in Granada, Spain from May 23 to 25 of 2002, the attendants concluded that prevention of mistreatment or trauma on a wound (dressing) and prevention of patient pain were considered the most important elements relating to the care of an injury. The removal of the dressings is the biggest cause of pain and hence a pain-free and non-trauma causing dressing is highly desirable .

FUNCTION OF PROTEOLYTIC ENZYMES IN BURN HEALING

Injuries of all types, including burns, all have something in common: they all produce the same physiologic response. The severity of such response varies with the degrees or types of wound.

Hyperemia is a physiologic response to trauma, which is followed by inflammation, a cicatrization pre-requirement, and subsequently by an edema, which usually delays healing. If the edema is too big, it can delay tissular metabolism thus increasing the possibility of infection, ischemia and hypertrophic scars. Accordingly it is advisable to use methods that reduce the edema.

An edema results from the accumulation of excess liquids and cell residues within the tissular spaces, while the elimination thereof depends on fluid drainage (for example, by applying pressure) and on the proteolysis, that is, increased removal of protein residues by proteolytic enzymes. It has been proved (Tribuna Médica [Medical Tribune] 354 1968) that enzymes from the *carica papaya* reduce to a minimum the edema associated with inflammation in the injuries during the cicatrization process, a fact that is directly related to a substantial reduction or absence of pain.

CURRENTLY AVAILABLE PRODUCTS FOR BURN TREATMENT

From homemade substances, herbs, Aloe vera, mucilage etc. to tannins, mercurial composition, and topical antibiotics comprise the wide range of substances used to treat skin lesions caused by burns (or abrasions), which further proves the absence of an unanimous consensus in this respect.

Home treatments such as coffee, onion, albumen and other substances from traditional knowledge are used in addition to a medical care based on antibiotics and scab forming substances such as mercurochrome (chromium mercury) which have to be associated with analgesics and lubricants for the aforesaid lesions.

Many other products have been used with varying results, such as cerium nitrate, iodine (which causes pain), tannins, rifampycin, and a three-part combined treatment consisting of silver nitrate plus mercurochrome plus tannic acid. This treatment is antiseptically weak and produces a scab that may be bacteria culture prone.

The use of topic antibiotic therapy for burns was not designed to treat recent superficial wounds, whose management target is quite different. Local antibiotic therapy should be reserved for those clinical instances in which the sepsis of the burn, due to its extension, will become a major problem. A patient with a recent superficial burn will not benefit from the use of antibiotics.

Some available products are:

-Mafenide: (sulfamilon) which is a methylated sulfonamide (sulfa group) effective against a wide range of bacteria, particularly the *clostridium,* which can penetrate the scab and cause a metabolic acidosis.

-Silver nitrate: an inorganic salt having poor injury penetration, helps remove the scab, narrow bacterial spectrum.

-Silver Sulfadiazine: comprises sulfadiazine and silver nitrate, penetrates the scab and is effective against the entire bacterial spectrum of burns.

-Gentamycin: used against the *pseudomona aeruginosa*, possesses quick bacterial resistance.

-Nitrofurazones: have a limited bacterial spectrum.

-Others: butesin picrate, metatitane (zinc oxide, titanium dioxide, vitamin A), aloe vera, epidermis growth factor (Cuban product) and other substances without therapeutic significance are found in the market.

-Use of proteolytic enzymes: The application of proteolytic enzymes on a burn wound with local sepsis is very useful as it disrupts coagulation, eliminates accumulated proteinaceous material that "protects" the bacteria from antibiotic action and thus increases the antibiotic effectiveness, while preventing an infection.

DESCRIPTION OF THE INVENTION

An object of the present invention is providing a topical composition for treating burns and sphacelus-causing skin injuries in connection with each one of the factors that produce a burn or superficial abrasion: pain, for which the thickening substance has been designed as a second skin (thus producing analgesia), inflammation, for which the proteolytic enzyme having a potent enzymatic debriding effect was designed, being these the basic features of gel.

Another object of the present invention is providing a composition that besides containing the abovementioned components may also comprise other components for secondary (non-primary) factors of burns, such as adding an antiseptic (chlorhexidine) in case an infection is suspected, urea for a better lubrication and an anesthetic (lidocaine) for painful injuries in adults and particularly in children.

The sepsis of a burn injury or burn is defined by Teplitz as: presence of bacterial organisms exceeding 100,000 colonies per gram of tissue in the burned tissue and which are actively invading the tissue underlying the burned zone (artz Chap. 17, Pg. 250).

For a short period of time after a burn, the wound remains generally sterile for up to 48 hours in average, the subsequent contamination comes from an external source, from the surrounding skin (saprophytes) and other sources such as respiratory sources and feces. It is important to recognize that the topical antibiotic therapy has been designed to control the sepsis of the burn and not for the regular treatment of small burns in which the sepsis is not a problem.

After acquiring a clear understanding of the concept of sepsis of a burn injury and the possibility or not of its appearance during the initial phase of a burn, the use of an adequate therapy is then reasoned. An overutilization of topical antibiotics may be counterproductive (overtreatment) for saprophyte bacterial proliferation.

Microbiologically speaking, a few hours after the burn, a superficial bacterial colonization begins with a great variety of organisms, in particular positive gram

cocci (mainly the staphylococcus). This colonization is started from the hair follicles and perifollicular tissue. After a period of 3 to 5 days the negative gram organisms become predominant, which initiate an invasion of the tissues underlying the burn. There is a lymphatic dissemination to the blood stream. There are some factors that predispose to bacterial overinfection such as vascular destruction, which prevents the supply of nutrients and immune cells, coagulation necrosis that increases with the overinfection and the vascular necrosis. It has been widely proved that burns inhibit the immune response (vascular necrosis).

The topical antibiotic therapy does not sterilize the burn. It simply reduces the number of bacteria while trying to let the immunological mechanisms of the host control the infection.

Given that flora in the burn is not completely eradicated, the handling is intended to allow the replacement of the skin layer.

When there is a bacterial colonization, the same is initiated superficially, where there is dead or necrotic tissue and advances progressively in depth. The greater the extension, depth and elapsed time, the bigger the chances are of infection. Age, nutritional and immunological condition of the individual, exposure to the surrounding environment, persistent inflammation, location of the wound and detritus on the wound are all important factors. A minor burn without any scab (detritus), clean tissues and isolated from the environment and without inflammation provides the best defense against overinfection. It is important to

realize that a topical antibiotic therapy on a burn is specifically targeted to control the appearance of sepsis on the burn and not as a regular treatment for small burns in which the infection is neither a threat nor a problem.

Currently there is a novel complementary approach different from the local therapeutic of burns, named HYDROGELS, directed to provide comfort, analgesia and pain relief in a quick time over the burned area, in addition to an anti-inflammatory and debriding effect. Such approach is neither an antibiotic therapy, nor is it indicated for scab removal. It relates to the formation of a soft, clear and colloidal layer that isolates the area, thus preventing any bacterial overinfection.

In line with the above concept, the new composition of the present invention was designed based on each one of the factors that produces a burn or superficial abrasion: pain, for which the thickener substance acting as a second skin was designed (thus producing analgesia); inflammation, for which the proteolytic enzyme having a potent enzymatic debriding effect was designed, being these the basic concepts of the gel.

In addition it is also possible to add new components for secondary factors (non-primary) of burns, such as the addition of chlorhexidine in case an infection is suspected, urea for better lubrication and anesthetic for painful wounds in adults or children.

The indications of the present invention are for the treatment of first degree injuries, superficial second grade injuries, not infected, that are not located in special areas and that cover less than 25% of extension.

The composition of the present invention has a new clinical focus with the following characteristics: it is a clear film that reduces inflammation, relieves pain, isolates the injured zone, features rheologic effect, prevents infection, is water absorbent and produces fast and efficient epithelialization.

It is a viscous clear gel comprised in a plastic tube designed to be applied and spread directly over the affected area. It is a new physiological stance in topical, symptomatic and preventive treatment in the pathology of superficial and non-infected local avulsions or burns.

International articles refer to the debriding and anti-inflammatory effect of papain, whose additional barrier or second skin effect is also used in the product.

In the design of the composition of the present invention, the combination, affinities and properties of the substances described, being focused on the pathology for which they were prepared, result in a specific formula for the treatment of the signs and symptoms exhibited in burns or avulsions.

This new composition offers comfortable use and application, mediate or immediate analgesia as well as a proteolytic debriding effect. It forms a clear coating that allows a direct view of the wound and has an apposite colloidal effect that exerts pressure isolating it effectively from the surrounding environment.

The reduction in liquid loss, easy handling and mobility of the affected zone lead to an actual prevention of overinfections and rapid tissue growth. The composition also offers other advantages such as its easy application and removal, being free

of adverse effects for the patient, being non-toxic for tissues, pain-free in its indicated application, not staining or decolorizing the injury and having a low cost.

MECHANISM OF ACTION

The composition creates a clear colloidal film over the injury covering the nerve endings (pain relief), isolating the injury from the external environment in order to prevent contact with harmful substances, maintaining the injury dry and applying pressure (apposite effect) in order to create a medium allowing fast and reliable cell regeneration; while the enzymatic action reduces inflammation, debrides and cleans the zone.

The market of products available for handling burns and superficial abrasions is somewhat vague: substances that are not designed to follow the course of the physiopathology of these wounds and that simply refresh, act as topical antibiotics or provide temporary relief without being tailored specifically for pain relief and anti-inflammation.

The basic concept underlying the composition of the current invention is to treat with each one of its components all the issues relating to the physiopathology of burns: the pain is produced by nerve endings being left exposed and the gel creates an external clear layer that covers the injury while the skin undergoes the natural and normal epithelialization process. This coating helps this process to be concluded faster as it provides a more suitable condition and medium (cleanliness, debridation, protection).

The inflammation occurs due to the physiological processes of reaction to injury (vasodilatation, cell migration, release of active substances such as histamine and serotonine), and the effectiveness of papain and the enzymes in the topical treatment and handling of the dermal inflammatory processes has already been proved.

Accordingly, it was found that the combination of protecting barrier-enzymatic substances in search of a new handling in the treatment of burns and superficial abrasions was ideal.

COMPONENTS OF THE COMPOSITION

a. Papain. It is a plant proteolytic enzyme from the *Carica papaya* that hydrolyzes peptidic, amidic and esteric bonds of proteins.

Its properties are having a good proteolytic activity, good thermostability, being thermosoluble, anti-inflammatory and exhibiting a debriding effect. In particular, it has a proteolytic activity from pH 3 to 9, a wide range of thermostability (up to 70° C), is poor in germ content and dissolves easily in water, and has a high effectiveness in viscous solutions.

Papain has many uses: as digestive substance that promotes or substitutes other digestive enzymes, used as an antihelminthic by destroying the protein cuticle of intestinal worms, and in the leather, tobacco and textile industries and as a meat softener. In wounds and burns it provides a proteolytic activity on dead tissues,

without attacking live tissues, causing enzymatic debridement and an optimal cicatrization. It has an inherent anti-inflammatory effect and it may be combined with certain antibiotics.

It is also used in biochemistry in breaking bonds and determining chemical structures of other proteins (as in the determination of human IgG).

Papain is a protease that catalyzes ester and peptide hydrolysis. The main amino acids comprising the same are: tryptophan, tyrosine, phenyl-alanine, histidine and arginine.

Papain is used in the composition of the present invention preferably in a range from 0.2 to 5 % by weight of the composition, preferably in an amount of 0.5% by weight of the composition.

b. Carboxymethylcellulose. This component is a synthetic resin derived from the acrylic acid. It is a thickener, emulsifier and interface coalescent (consistence). It provides the following features to the composition of the present invention:

-Protecting barrier, or second skin that isolates the wound while the papain acts.
-Provides the necessary stabilization as well as filmogenous and physiologically inert agents.
-Good antibacterial barrier.

This component is a well-known product and it is used in several industrial production fields such as: foodstuffs, textiles, detergents, cosmetics, paints,

adhesives, ceramics, toothpaste, leather, etc. It is a cellulose-derived anionic polymer with the following properties:

a. Dissolves easily in cold or hot water.
b. Acts as a thickening agent, suspension agent and suspension stabilizer.
c. Retains water thus contributing to keep dry the underlying wound.
d. Acts as a filmogenous agent that is oil, fat and organic solvents resistant.
e. Acts as binder and as colloid protector.
f. Is a rheologic control agent.
g. Is physiologically inert, an essential property for the effect sought.

The CMC solution does not coagulate when heated, as there is only a reduction in its viscosity when the temperature exceeds 40°C. It has a high resistance to microbiologic attacks and when stored for long periods of time, the use of preservatives is recommended to avoid viscosity reduction and degradation. It has a broad range of stability, from pH 4 to pH 9, being preferred a neutral pH .

The preferred range of use of this component is from 1.0 to 4 % by weight of carboxymethylcellulose gel and the gel carboxymethylcellulose is present in a range from 71.5 to 77.5 % by weight of the composition.

c. CARBOPOL. This a high molecular weight synthetic resin, polymerized with a hydrophobic monomer, obtaining a cross-linked polymer extracted from the acrylic or polyacrylic acid. Its chemical name is carboxypolymethylene.

It is mainly used as a thickener and emulsifier, its function is maintaining the homogenization of the preparations, stabilizing emulsified systems against sedimentation or separation, absorbing the respective interface (oil-water). CARBOPOL coalesces rapidly the application of the product with its emulsion stabilization and thickening effect by giving it consistency .

Its main features are:

a. Forming a barrier that protects the skin from new potential external irritants.

b. Cleaning and removing undesired oily substances.

c. Distributing uniformly the composition over the skin.

d. Accelerating the stabilization of the composition.

e. Being stable for two years at room temperature.

f. Requiring low concentrations of CARBOPOL to obtain the desired effect.

g. Eliminating the need for emulsifying soaps.

h. Being clear and not producing any skin irritation.

i. In the event of coming in contact with the eyes, it may cause minor irritation.

j. Not poisonous when ingested.

There are many types of carbopols, the most important are Carbopol 941, Carbopol 940, Carbopol 934, Carbopol ultrez 10, Carbopol etd-2020. Carbomer polymers have been used for rheological control (structuring agents) in lotions, creams and gels. Polymer molecules have the unique ability of increasing the viscosity of liquids in which they are dissolved (dispersed), even in very wet

concentrations. This is due to the volume expansion ability (water absorption) of carbomer microgels.

The viscosity increase capacity of a polymer depends on its "intrinsic viscosity". The unit employed to express "Intrinsic viscosity" is dL/g. Factors that affect intrinsic viscosity of carbomer polymer are: pH, types of electrolytes and ion concentration.

Microgel particles in polymers increase the viscosity of a solution by means of two mechanisms: 1) increasing viscosity in a direct ratio to the polymer's swelling and 2) increasing viscosity by microgel stiffness.

The preferred range of use for this component in the composition is from 1.5% to 2.5% by weight of Carbopol gel, and Carbopol gel is present in an amount from 22-28% by weight of the composition.

Optionally, the composition comprising the three components a., b. and c. mentioned above may also include an analgesic in order to bock nerve conduction, when locally applied. Lidocaine is the most stable local anesthetic and consequently the most commonly used nowadays. It is currently used in anesthetic solutions for topical application and for mucous membranes, and also as injectable anesthetic, infiltration anesthesia, and in cardiology as a modifier of cardiac rhythm. It is used in the composition in a range varying from 1% to 5% by weight of the composition.

EXAMPLES OF COMPOSITIONS FOR DIFFERENT TYPES OF APPLICATIONS

EXAMPLE 1

In a first embodiment, the composition of the present invention is prepared in three steps:

a) First, a CARBOPOL gel is prepared, which is present in the composition in 25% by weight.

b) Secondly, the carboxymethylcellulose gel is prepared, which is present in the composition in 74.5% by weight.

c) Finally, papain is added in an amount of 0.5% by weight to the composition.

a. CARBOPOL GEL. This gel is prepared according to the following composition:

Carbopol	2.00%
Triethanolamine	2.23%
Distilled Water	95.77%.
Total CARPOBOL gel	100.00%.

b. CARBOXIMETHYLCELLULOSE GEL. This gel is prepared according to the following composition:

Carboxymethylcellulose Sodium	3.00%
Propyl Parebene	0.50%

Methyl Parabene	0.50%
Distilled Water	96.00%.
Total carboxymethylcellulose gel	100.00%.

c. ACTIVE PRINCIPLE. PAPAIN

PAPAIN	0.50%

Formula of standardized manufacturing lot: 5000 g

RAW MATERIALS	AMOUNT
PAPAIN	25 grams,
CARBOPOL GEL	1250 grams,
CARBOXYMETHYLCELLULOSE SODIUM GEL	3725 grams.
TOTAL AMOUNT RAW MATERIALS	5000 grams.

According to the abovementioned percentages, the amounts necessary for manufacturing the composition subject matter of the present invention are detailed below:

a. CARBOPOL GEL: 1250 g

RAW MATERIAL	AMOUNT
Carbopol	25.0 grams,
Triethanolamine	28.0 grams,

Distilled water	1198.0 grams
Total Raw Materials	1250 grams
b. CARBOXYMETHYLCELLULOSE SODIUM GEL:	3725 grams.
Carboxymethylcellulose Sodium	112.0 grams,
Propyl Paraben	19.0 grams
Methyl Paraben	19.0 grams,
Distilled Water	3576.0 grams
c. PAPAIN	25 grams

2. Example of the manufacturing process:

a. CARBOPOL GEL

1. Select a 2 kg capacity stainless steel container.
2. Pour the distilled water in the stainless steel container.
3. Slowly add the triethanolamine.
4. Start the stirring process with a stainless steel stirrer.
5. Keep stirring while the carpobol is slowly added.
6. Pour into a mixer, stir at minimum speed for about 15 min. until completely dissolved and a clear gel is obtained.

b. CARBOXYMETHYLCELLULOSE GEL

1. Select a 5 kg capacity stainless steel container.

2. Pour the distilled water in the stainless steel container.

3. Slowly add the carboxymethylcellulose.

4. Start the stirring process with a stainless steel stirrer.

5. Keep on stirring while slowly adding the propyl paraben.

6. Keep on stirring while adding the methyl paraben.

7. Warm this mixture until reaching a temperature of 50 to 60°C, while constantly stirring.

8. Stop heating and keep stirring until the mixture reaches room temperature.

9. Pour into the mixer and stir at minimum speed until the mixture reaches a temperature of 17°C.

c. PAPAIN

1. In a stainless steel container pour the CARBOPOL GEL.

2. Slowly add the CARBOXYMETHYLCELLULOSE GEL.

3. Start the stirring process with a stainless steel stirrer.

4. Keep on stirring while slowly adding the PAPAIN.

EXAMPLE 2

In a second embodiment, a composition having the following components is provided:

a. First substance: A proteolytic enzyme, in this case the papain derived from *carica papaya*, whose dedriding and anti-inflammatory advantages are used for the treatment of injuries.

b. Second substance: CARBOPOL.

c. Third substance: carboxymethylcellulose sodium salt.

d. Forth substance: local anesthetic drug.

The composition or quantitative formula of the product is prepared in three steps and it is described as follows:

1. CARBOPOL GEL	25%
2. CARBOXYMETHYLCELLULOSE GEL	72.5%
2. LIDOCAINE	2.0%
3. PAPAIN.	0.5%

The composition of the present invention is prepared in three steps:

a) A CARBOPOL gel is first prepared, which comprises 25% by weight of the composition .

b) Then, preparation is made of the carboxymethylcellulose gel, which comprises 72.5% by weight of the composition.

c) Finally, papain and lidocaine are added in amounts of 0.5% and 2%, respectively, by weight of the composition.

a. CARBOPOL GEL. This gel is prepared according to the next composition:

Carbopol	2.00%,
Triethanolamine	2.23%,
Distilled Water	95.77%.
Total CARBOPOL gel	100.00%

b. CARBOXYMETHYLCELLULOSE GEL. This gel is prepared according to the following composition:

Carboxymethylcellulose Sodium	3.00%,
Propyl Paraben	0.50%,
Methyl Paraben	0.50%,
Distilled Water	96.00%.
Total carboxymethylcellulose gel	100.00%

c. ACTIVE PRINCIPLE. PAPAIN

Papain	0.50%.

d. ANESTHETIC.

Lidocaine	2.00%.

2. Example of the manufacturing process:

a. CARBOPOL GEL.

1. Select a 2 kg capacity stainless steel container.

2. Pour the distilled water in the stainless steel container.

3. Slowly add the triethanolamine.

4. Start the stirring process with a stainless steel stirrer.

5. Keep on stirring while slowly adding the carbopol.

6. Pour into the mixer, stirr at minimum speed for about 15 min until dissolution is complete and a clear gel is obtained.

b. CARBOXYMETHYLCELLULOSE GEL

1. Select a 5 kg capacity stainless steel container.

2. Pour the distilled water in the stainless steel container.

3. Slowly add the carboxymethylcellulose.

4. Start the stirring process with a stainless steel stirrer.

5. Keep on stirring while slowly adding the propyl paraben.

6. Keep on stirring while the methyl paraben is added.

7. Warm this mixture until reaching a temperature of 50 to 60°C, while constantly stirring.

8. Stop heating and keep stirring until the mixture reaches room temperature.

9. Pour into the mixer and stir at minimum speed until the mixture reaches a temperature of 17°C.

c. PAPAIN AND LIDOCAINE

1. Pour the carbopol gel into a stainless steel container.

2. Slowly add the carboxymethylcellulose gel into the container.

3. Start the stirring process with a stainless steel stirrer.

4. Keep on stirring while papain and lidocaine are slowly added.

Preparation of the composition of the present invention with chlorhexidine and urea is similar to and follows the same parameters of the procedure described above.

EXAMPLE 3

COMPARATIVE CLINICAL RESULTS WITH EXISTING PRODUCTS .

A clinical evaluation of the product was made, which contained patient data, a brief anamnesis, a description of the injury and a monitoring time chart with the variables PAIN, INFLAMMATION and DEBRIDING EFFECT.

In addition presence of overinfections was investigated, which was negative.

STUDY GROUP: 44 Patients having a burn or avulsion diagnostic and meeting the requirements to apply the composition of the present invention were selected.

ADMINISTRATION SCHEME, DOSES, ROUTE AND FREQUENCY

The product under study is for cutaneous application only, and once an injury has been made, its application is made in topical dosages every 2 hours, modifiable once the skin renovation process is noted.

The comparative study was conducted with the composition of the present invention and aloe vera (a substance derived from the aloe vera plant,

recommended and advertised for handling burns and having a similar appearance to the composition of this application), both in gel presentation.

No antibiotic cream was used in this study, since the object was not infected injuries or areas already subjected to a bacterial growth process.

Most treated injuries varied from 1 to 10% in extension, excluding some patients who were applied the present composition in extensive burns of up to 30%. All injuries were of first and second grade according to their depth, which are those likely to heal with these products.

No important complications were observed, although some burns treated with Aloe Vera frequently followed an infectious development in these injuries.

The products were applied according to the following evaluation times:

- 0 Hours: Initial clinical evaluation.
- 6 Hours: during this period of time, the symptoms for these specific injuries are felt stronger.
- 24 Hours: At this time all first and second degree burns and covering small areas have a stabilized symptomatology under a natural process and their injury resolution starts.
- 72 Hours: This type of injuries under a natural and regular development are in recovery, missing a high percentage of signs and symptoms.

ALOE VERA RESULT ANALYSIS:

As an adjuvant in the initial symptomatology, it refreshes and soothes and as part of the general measures, it has some level of efficiency without being the ideal product in connection with the evolution thereof.

In general, patients believe the product to be "refreshing, good" and to aid in the initial comforting of the wound, while during the following hours, it does not have any kind of clinical incidence, all related with the natural evolution of the injury, its extension, depth and localization. 50% of the patients consider the product to be good, between good and excellent 10%, and average 12%.

Physicians' opinions are generally good 52%, improves patient's comfortableness, excellent 10% and 30% prevents greater inflammation. Most medical reports declare persistent discomforts related to pain and inflammation, and an aqueous appearance of the Aloe.

EVOLUTION OF PAIN:

Most of the patients had severe pain at the time of the initial evaluation.

After 6 hours of starting the handling with Aloe, the pain had substantially subsided, although some patients still had intense pain (13%.)

After 24 hours: some patients still report moderate to mild pain and 70% without pain.

After 72 hours: 5% of the patients with moderate pain, 18% mild and 77% without pain.

EVOLUTION OF THE INFLAMMATION:

Most of the injuries were small.

After 6 hours: One patient has severe inflammation and 33% have mild inflammation.

After 24 hours: 30% remain with mild inflammation and moderate in almost 50% of the group.

After 72 hours: 36% of the patients still report mild inflammation.

CLEANSING EVOLUTION : Not significant.

ANALYSIS OF RESULTS WITH THE COMPOSITION OF THE EXAMPLE 1:

The opinion rendered by the patients with respect to the product being in a superlative and excellent ranking is 48%, good 42%, 10% of patients did not provide any opinion, there were no average rankings . The study reports some cases of mild discomfort upon application and fast pain relief throughout the study. Epithelialization and deinflammation occur after a short period of time.

The physicians' opinions also are in superlative ranking, very good and excellent 32%, and good 46%; magnificent analgesia, efficient product, easy to handle product and used in wider and more serious injuries.

EVOLUTION OF THE PAIN WITH THE COMPOSITION OF EXAMPLE 1:

After 6 hours: 35% of the patients have severe pain at time zero, and six hours later, this percentage is reduced to 3%.

After 24 hours: pain is mild and 87 % do not have any pain.

After 72 hours: only 3% of the patients have a mild degree of pain and 89% do not report pain.

EVOLUTION OF THE INFLAMMATION WITH THE COMPOSITION OF EXAMPLE 1:

After 6 hours: one patient with severe inflammation, 35% with mild inflammation and 46% without inflammation.

After 24 hours: only one patient reports severe inflammation, most (78%) do not have inflammation.

After 72: 2% report mild inflammation and 85% do not have inflammation.

These results confirm the effectiveness of the product for pain an inflammation. As it may be noted, the compositions subject matter of the present invention have superior analgesic, protective, debriding, and anti-inflammatory effects over those of the State of the Art.

The above examples should not be construed as limiting the scope of the present invention and the scope of the same is determined by the claims provided below.